

### **REMARKS/ARGUMENTS**

Claims 1-5 and 7-29 are pending. Claims 10-14 and 20-28 are withdrawn from consideration. Claim 1 has been amended; claim 6 has been canceled; and claim 29 has been added. No new matter has been added.

In the Office Action dated January 25, 2008, the Patent Office set forth three separate art-based claim rejections. Claims 1-2, 5-9 and 15 were rejected as allegedly anticipated under 35 U.S.C. § 102(e) by U.S. Patent No. 6,552,172 to Marx et al. (Marx). Claims 1-9 and 15 were rejected as allegedly rendered obvious under 35 U.S.C. § 103 over U.S. Patent App. Pub. No. 2003/0219785 to Hallahan et al. (Hallahan). And claims 1-9 and 15-19 were rejected as allegedly rendered obvious over Hallahan in view of U.S. Patent No. 7,220,401 to Lanza et al. (Lanza) in view of Marx. Each of these rejections is discussed in turn.

#### **Anticipation Rejection of Claims 1-2, 5-9 and 15 Over Marx**

The entirety of the rejection of these eight claims over Marx states: “Marx teaches fibrin (organic protein) nanoparticles coupled o(or covalently bonded) to agents wherein the agents may be thrombin (col. 2, 7) or other pharmaceuticals (col.7).” (Office Action dated Jan. 25, 2008, at 2.)

In an effort to advance prosecution, Applicants have amended claim 1 to include the elements of claim 6. Notably, the rejection did not point out any portion of Marx that taught the limitations of that now-canceled dependent claim; Marx does not teach or suggest the elements recited in amended claim 1.

As a starting point, Marx is completely different from the subject matter of the pending claims. Marx does not teach nanoparticles attached to thrombin. Rather, the thrombin in Marx is merely a reagent for the preparation of fibrin, in the reaction with fibrinogen and Factor XIII.

This common enzymatic reaction is responsible to the formation of a highly crosslinked fibrin, which can be attached to a number of agents (as detailed in column 7 cited in the Office Action), and thrombin is not specifically disclosed in connection with those agents.

The differences between the composition of Marx and the present composition with respect to type of particles, the role of thrombin, and particle size are summarized in the table below.

Property	Marx	Embodiments of the Present Application
Type of particles	Heavily crosslinked fibrin (at least 30% crosslinking)	Not directed to fibrin.  Mainly (at least 90%) a nanoparticle core with a small percentage of free thrombin (not crosslinked)  As claimed in claim 1 (formerly claim 6), the nanoparticles may be selected from the group consisting of magnetic iron oxide-containing nanoparticles, albumin nanoparticles, solid or hollow silica nanoparticles and nanoparticles made of organic polymeric core coated with a silica shell, optionally having magnetic layer interposed between said core and said silica shell.
Role of Thrombin	A reagent for the formation of the fibrin nanoparticles (FNP). The thrombin is not conjugated to the FNP	Conjugated to the nanoparticles of the invention.
Particle size and uniformity	Particles are not uniform. At least 2 populations exist. Particle diameter ranges from 200 nm to 2000 nm (i.e. not a "nano particle")	Particles are substantially uniform: only one population exists.  Particle diameter is smaller than 100 nm (i.e., a "nano particle")

The present invention does not relate to fibrin, and it is neither disclosed nor hinted at in the present application. Fibrin is further not intended as the thrombin-conjugated nanoparticle.<sup>1</sup> In fact, the only reference to fibrin in the present application is stating that the present composition can be used in the preparation of a “*fibrin-based biological sealant*.” (E.g., PCT Pub. No. 2004/045494 at 6.) Fibrin is not part of the claimed subject matter because it is intended that the fibrin formation will occur in the bleeding site, thereby forming the desired blood clot and stopping the bleeding. Using fibrin, or crosslinking thrombin, as the nanoparticle of the present invention would result in the premature formation of biological glue, which is most undesirable for the purpose of the invention, and would likely prevent a reaction with the blood particles for subsequent clotting.

Notwithstanding the fundamental differences between Marx and the presently claimed subject matter and in an effort to advance prosecution, Applicants have amended claim 1. Amended claim 1 now includes the elements previously recited in claim 6. Marx does not teach or suggest the nanoparticles that are selected from the group consisting of magnetic iron oxide-containing nanoparticles, albumin nanoparticles, solid or hollow silica nanoparticles and nanoparticles made of organic polymeric core coated with a silica shell, optionally having magnetic layer interposed between said core and said silica shell. Not only does Marx not disclose or teach nanoparticles attached to thrombin, but it also does not disclose or teach the types of nanoparticles recited in claim.

Applicants therefore respectfully request withdrawal of the rejection over Marx.

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<sup>1</sup> Although not specifically referenced in the Office Action, Marx does refer to FITC-albumin in Example 6. But this mere mention of “FITC-albumin” does not teach the claimed subject matter, which includes albumin as a nanoparticle conjugated to thrombin as in amended claim 1 or as a spacer arm as in claim 8.

**Obviousness Rejection of Claims 1-9 and 15 Over Hallahan**

Hallahan is not prior art.

Hallahan is the 18-month publication of a now-abandoned U.S. patent application, App. No. 10/355,824. The '824 application was filed on January 31, 2003, and "is based on and claims priority to U.S. Provisional Application Serial No. 60/353,306, . . . which was filed Feb. 1, 2002." The provisional application, however, does not provide an enabling written description of the portions of Hallahan cited in the Office Action. Thus, Hallahan's date for the purposes of prior art is the date of the filing of the nonprovisional application (i.e., Jan. 31, 2003) and not the date of the provisional application (i.e., Feb. 1, 2002).

Under 35 U.S.C. § 119(e), a nonprovisional application is entitled to the benefit of priority to the filing date of a provisional application if the provisional application describes and enables the nonprovisional application as required by 35 U.S.C. § 112, first paragraph. That is, any "new matter" added to the nonprovisional application is only prior art under § 102(e) as of the filing date of the nonprovisional application. Applicants have examined the provisional application upon which Hallahan relies, and it appears to be a printout of a presentation. There is essentially no accompanying explanation or explication of the terse, laconic disclosure on each slide. Furthermore, the portions of Hallahan cited on page 4 of the Office Action do not appear in the slideshow submitted as the provisional application. For example, the provisional application does not contain an adequate description of an active agent including thrombin, a paramagnetic material made from iron oxide, and/or a linker arm made from albumin, etc. That is, the provisional application does not provide an adequate disclosure under § 112, first paragraph, and Hallahan is thus prior art only as of its filing date, Jan. 31, 2003.

The presently pending claimed subject matter is entitled the benefit of a priority date that antedates Hallahan. At a minimum, the presently claimed subject matter is entitled to the benefit of priority to a provisional application, U.S. App. No. 60/427,545, which was filed on Nov. 20, 2002. For example, iron oxide nanoparticles are described on pages 16-17 of the provisional application; albumin nanoparticles are described on pages 17-18; silica nanoparticles are described on pages 18-19; thrombin binding to nanoparticles is described on pages 23-25; physical binding thrombin-albumin is described on page 25; and covalent binding of thrombin is described on page 25. Various relevant examples provide support for using these systems, as described on pages 26-53. These and other portions of the 55-page disclosure disclose the claimed subject matter.

Because Hallahan is not prior art (i.e., because its priority date postdates the priority date for the presently pending subject matter), the rejections over Hallahan, either alone or in combination with Marx and Lanza, should be withdrawn.

Regardless, Applicants note that Hallahan describes a method of identifying cancer cells using paramagnetic particles linked to an active agent. These paramagnetic particles are mobilized via a magnet to the required site. Thus, the purpose and composition of the cited reference completely differ from those of the presently claimed subject matter. Hallahan does not exemplify linking of thrombin to its paramagnetic particles, either directly or via a spacer. Thrombin, furthermore, is merely listed among other possible toxins. And although thrombin is listed among many other possible toxins, Hallahan provides no motivation to use thrombin as the active agent.

Even if a person of ordinary skill in the art would have been motivated to link thrombin to the paramagnetic particles, Hallahan would be teaching away from the purpose of the present

invention, in which the thrombin may be covalently linked to the particles. Hallahan aims at reaching specific cells and then releasing the active molecule (for example, releasing a toxin to kill a targeted cell). Thus, upon reading Hallahan's publication, a person skilled in the art would not expect that the active molecule be conjugated (e.g., covalently attached) to the surface of the nanoparticles, because Hallahan requires the release of the toxin upon reaching the target site. Hallahan, aimed at releasing an active agent, could not have motivated anyone to devise the present composition, which does not permit the release of thrombin and requires the conjugation of the thrombin to the nanoparticles so that it can complete its "mission": clotting and stopping any bleeding.

Furthermore, the Office Action appears to misconstrue the role of albumin in the cited art. Although the Office Action states that the albumin may be used as a spacer, a thorough review of Hallahan finds no such support. As cited in the Office Action and confirmed by Applicants, the only reference to albumin is in paragraph 148, where it is mentioned as a possible active ingredient. Thus, while in Hallahan the albumin is not linked to the thrombin at all, in the present invention, albumin is actually used for its high physical affinity to thrombin.

New claim 29 further defines the claimed invention. It specifies that the thrombin is either covalently attached to the nanoparticles or to the spacer arm (which clearly is not the case of Hallahan) or that it is physically attached to albumin (a spacer-arm) which is covalently linked to the nanoparticles (which again is not the case of Hallahan). It is believed that the combination of thrombin-albumin has an exceptionally high affinity, which is particularly suitable for the purpose of the present invention.

Applicants therefore respectfully request withdrawal of the rejection over Hallahan.

**Obviousness Rejection of Claims 1-9 and 15-19 Over Hallahan in View of Lanza and Marx**

As detailed in the previous sections, Hallahan is not prior art and Marx does not teach or suggest the limitations in amended claim 1. For those reasons, the rejection over Hallahan in View of Lanza and Marx should be withdrawn as well.

Regardless, Applicants note that Lanza is completely irrelevant to the presently claimed subject matter (as well as to Hallahan and Marx). Lanza discusses a liquid colloidal composition, from which drops of emulsion were prepared. Neither Marx, nor Hallahan nor Lanza disclose the preparation of compositions acting as biological glues or as blood-clogging agents. Therefore, a person skilled in the art would not have found it obvious to use them – either individually or in combination – in preparation of such agents.

Furthermore, the additives listed in pending claims 16-19, such as dispersants, Ca salts, Factor XIII and antifibrinolytic agents, may be added in order to promote the formation of blood clots. The subject matter recited in these claims, therefore, cannot be visualized or readily obtained based on Marx, Hallahan and Lanza, which, as disclosed above, neither teach nor hint of the preparation of blood clotting agents.

A purpose of Lanza appears to be the discovery of thrombosis (blood clot) whereas, quite in contrast, the purpose of the present invention is to create such a blood clot. Thus, again, Applicants fail to see how can this reference, either alone, or in combination with the other references, be linked to the present invention.

Applicants therefore respectfully request withdrawal of the rejection over Hallahan in view of Marx and Lanza.

### **Conclusion**

Applicants submit that claim 1 and its dependents (i.e., all non-withdrawn claims) are in condition for allowance. If any small matter remains outstanding, the Examiner is requested to

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telephone Applicants' representative. Prompt reconsideration and allowance of this application is requested.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140.

Respectfully submitted,

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